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CHALLENGES AND RESTRICTIONS IN ASTHMA MANAGEMENT

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ABSTRACT

Asthma is a complex disease and is no more considered as a single entity. It is an umbrella of term constituting many phenotypes, each varying in its clinical presentation and response to treatment1. Each phenotype requires specific approaches for control. But for an average clinician it is not practical to differentiate between phenotypes at least in the early stages of presentation. Hence all asthma patients pass through an ordeal of guideline based management.

INTRODUCTION

Asthma is a complex disease and is no more considered as a single entity. It is an umbrella of term constituting many phenotypes, each varying in its clinical presentation and response to treatment [1]. Each phenotype requires specific approaches for control. But for an average clinician it is not practical to differentiate between phenotypes at least in the early stages of presentation. Hence all asthma patients pass through an ordeal of guideline based management. It is reported that only 68% of patients get adequate control if treated under GINA guidelines. Hence more than 30% remains symptomatic and requires individualized management for control. If this subset of patients can be identified at the onset we can offer them early control and reduce morbidity. This also has a significant impact on cost of treatment.

Specific treatments for asthma are unlikely to benefit all patients with asthma, but more likely target specific phenotypes. For example new approaches are needed for the

treatment of severe asthma, but patients need to be endotyped so that they can be directed for specific treatments. Severe asthma is a phenotype which includes three distinct types. They are the untreated severe asthma, difficult to treat severe asthma and therapy resistant asthma. So it is important that we recognize these entities as early as possible and subject them to individualized approach. Going further it is now understood that therapy resistant asthma comprises of two distinct entities such as patients who achieve good control but with maximum dose of the drug and those who are not controlled in spite of the maximum dose of drugs. Patients who do not respond to treatment remain a substantial part of the asthma burden. These patients again deserve separate strategy for management. More specifically, targeted novel treatments are needed in this group of patients.

Focus on a specific target in a well defined phenotype of asthma is more likely to lead to a more successful treatment outcome than in a non phenotyped group. This can be accomplished by further grouping the phenotype based on pathophysiological characteristics. The addition of known pathophysiological mechanisms into the phenotypic characterization has been called endotyping [2].

Presence of eosinophils in sputum can be considered as a marker for targeted treatment. Sputum eosinophilia is defined as presence of 2% or more eosinophils in sputum samples. This is found in 36% of patients with asthma not treated with inhaled corticosteroid and in 17% of patients taking inhaled Corticosteroids [3]. Measurement of sputum eosinophils could be used to guide asthma treatments [4], resulting in improved asthma control and fewer exacerbations. If sputum eosinophil count is less than 1% corticosteroid can be discontinued and if between 1-3% the existing steroid dose can be maintained and if it is more than 3%, that patient need to have higher dose of inhaled steroids or addition of oral steroids [5]. Patients with a subphenotype of severe asthma with recurrent exacerbations and sputum eosinophilia would benefit from anti-interleukin-5 treatments [6].

Another group is the neutrophil predominant endotype where the predominant cell type is neutrophils. Here the eosinophil count may be less than 1%.Neutrophilic asthma is predominant in patients with severe refractory asthma. Neutrophilic response might be indicative of a disease mechanism that is not driven by T-helper-2 cells and most likely, non-steroid responsive asthma. Bacterial colonization in the airways of patients with severe

asthma and oral corticosteroid treatment can contribute to neutrophilic asthma. There is yet another group of patients with asthma who have mixed neutrophilia and eosinophilia in sputum and they have worse lung function, increased frequency of daily wheeze, and increased health-care utilization compared to other patients. Patients with poorly controlled asthma and a predominant sputum neutrophilia may benefit from antibacterial agents such as macrolides [7]. This is a readily identifiable group and comprises 10% of the difficult to treat asthma phenotype.

Another subtype in the category of refractory asthma is those with airway hyper responsiveness (AHR). Measurements of AHR can be used as a tool to titrate anti-inflammatory therapy. It is found that increasing the dose of corticosteroid in response to a reduction in methacholine PC_{20} appeared to improve asthma control. Bronchial thermoplasty is a novel mechanical therapy that has an effect on AHR. This treatment heats the proximal segmental airways in asthma through the application of a radiofrequency energy that breaks and damages the airway smooth muscle. Thermoplasty also reduced the amount of airway smooth muscle. With bronchial thermoplasty a 32% reduction was reported in the rate of severe exacerbations.

MANAGEMENT

On review of the above facts it is clear that the phenotype of severe asthma is not a single entity when pathophysiological features are considered. Hence the management of this entity needs different approach. Targeting the pathophysiological characteristic with new molecules or mechanical therapy can influence the control. For example, asthma exacerbations could be reduced by 40% using a highly targeted monoclonal antibody to IL-5 (Mepolizumab)[6] in patients with marked eosinophilic inflammation. Mepolizumab significantly reduced exacerbation rates [8], improved Asthma Quality of Life Questionnaire (AQLQ) scores, and allowed oral prednisolone doses to be successfully reduced in refractory eosinophilic asthma. Other alternatives to oral corticosteroids in patients with a persistent sputum eosinophilia are methotrexate and oral cyclosporine. But both these drugs are known to produce potential life-threatening side-effects such as myelosuppression, and hepatotoxicity.

Neutrophilic asthma is more common in smokers and obese females [9]. There is evidence that macrolides may specifically target neutrophilic airway inflammation. Mepolizumab

which is effectively used in eosinophilic inflammation do not have an impact on AHR. However AHR is used to titrate antiinflammatory therapy. It is found that stepping up corticosteroid therapy in response to a reduction in methacholine PC_{20} appeared to improve asthma control.

Bronchial thermoplasty is a novel mechanical therapy that heats the proximal segmental airways in asthma through the application of a radiofrequency signal. Early clinical studies in mild-to-moderate asthma demonstrated an effect of bronchial thermoplasty upon AHR that persisted over 2 years.

Endotype	Characteristics	Treatment
Eosinophilic asthma	Recurrent exacerbations; sputum eosinophils; Steroid-dependent asthma	Anti-interleukin-4 receptor α (Dupilumab), Anti-interleukin-5 (Mepolizumab)
Neutrophilic asthma	Sputum neutrophils	Macrolide antibiotics (Azithromycin)
Asthma with airway hyperresponsiveness	Poor control, Reduced Methacholine PC20	Anti-interleukin-5 (Mepolizumab), Bronchial Thermoplasty

Table-1: Targeted therapy based on endotyping

CONCLUSION

Severe asthma poses a significant health care burden accounting for up to 50% of the asthma budget. Managing patients with severe asthma is complex and requires a multidisciplinary approach and a standardized protocol. The difficult to treat group requires further typing based on pathophysiological characteristics in addition to their phenotypic variability. This should enable the physician to better target these characteristic and individualize the management.

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